Marvel.

Derivatives Of Cyclopentanone

DERIVATIVES OF CYCLOPENTANONE

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY CARL SHIPP MARVEL

ENTITLED DERIVATIVES OF CYCLOPENTANONE

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ARTS

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In Charge of Thesis

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Recommendation concurred in:*

Committee
on
Final Examination*

*Required for doctor's degree but not for master's.

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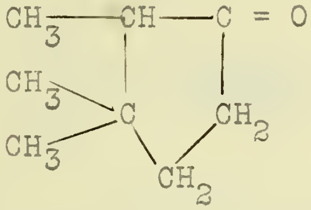
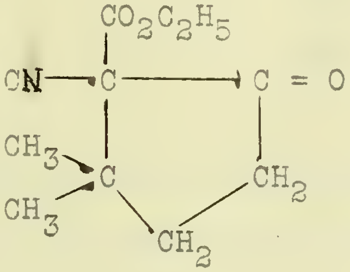
I. Introduction

Several years ago Noyes and Shepard[1] prepared the ketone $C_8H_{14}O$ by a series of reactions beginning with camphor. To this ketone they ascribed the formula:



In an attempt to prepare this ketone in a manner that would conclusively demonstrate its structure, Noyes[2] prepared the compound dimethyl-cyano-carboxethyl-cyclopentanone and proved its structure to be:



In a further study of this ketone a very unusual hydrolysis was observed. By hydrolysing with acid a carbon atom is removed from the ring and an oxygen atom is substituted in its place. Hydrolysis with an alkali gives the salt of an aliphatic hydroxy-acid. On account of this peculiar behavior of the ketone a study of its derivatives was undertaken.

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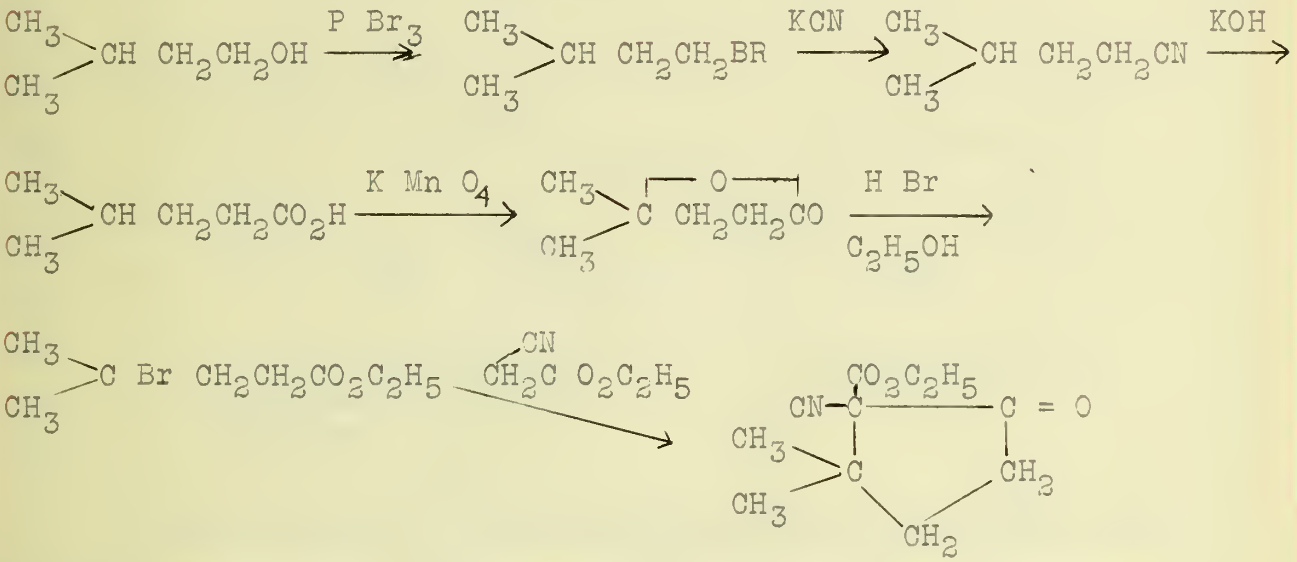
[1] Noyes and Shepard, Am. Chem. J. (1889) 22, 264.
[2] Noyes, Am. Chem. J. (1899) 22, 260.

II. Historial and Theoretical

The first synthesis[1] of 3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone was accomplished by the following series of reactions starting with isoamyl alcohol:



3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone

The hydrolysis of this ketone was expected to yield 3,3 dimethyl-2-carboxyllic-cyclopentanone, by the saponification of the carboxethyl and nitrile groups to form a dibasic acid, with the subsequent loss of carbon dioxide. Noyes[2] observed that the ketone did not hydrolyse in this manner, but instead a carbon atom was removed from the ring and replaced by an oxygen atom. Hydrolysis with dilute hydrochloric acid yielded acetic acid, isocaprolactone, and carbon dioxide. Hydrolysis with alcoholic potash yielded the potassium salts of malonic and γ-hydroxy-isocaproic acid. This decomposition is related to the acid decomposition of

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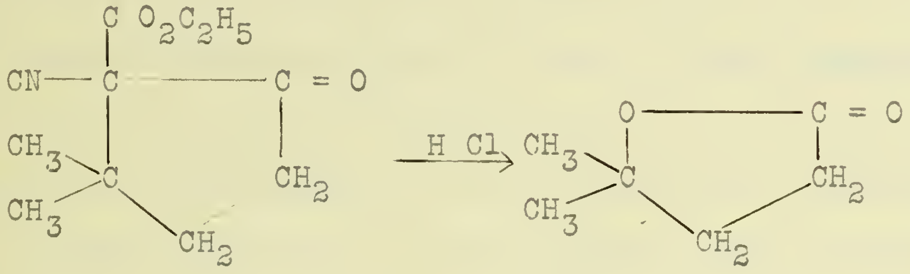
1. Noyes, J. Am. Chem. Soc. 23, 392.
2. Noyes, J. Am. Chem. Soc. (1901) 23, 396.

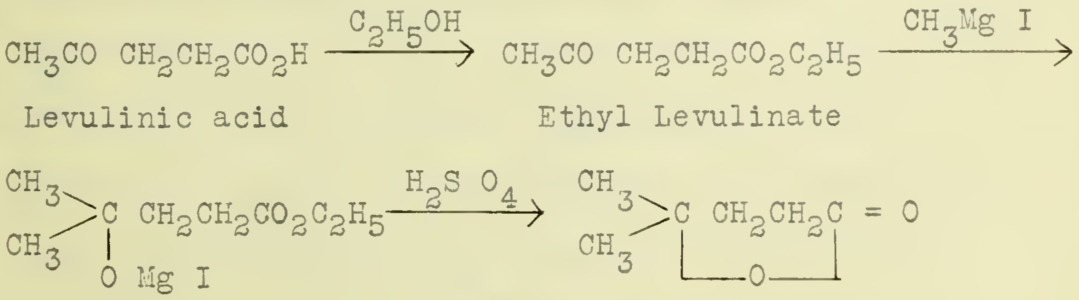
acetoacetic ester and its derivatives. It is, however, the only case described in the literature in which a carbon atom is displaced from a five carbon ring and replaced by an oxygen atom by a simple process of hydrolysis. The relations may be more clearly seen from the structural formulae:



3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone.

Isocaprolactone

The synthesis of dimethylcyanocarboxethylcyclopentanone first worked out was very long and tedious and the yields were poor. Noyes and Hewes[1] have worked out a more satisfactory method of preparing isocaprolactone which shortens the synthesis of the ketone. The ethyl ester of levulinic acid is treated with methyl magnesium iodide in ether solution and the addition product decomposed with dilute sulphuric acid.



$$CH_3CO\ CH_2CH_2CO_2H \xrightarrow{C_2H_5OH} CH_3CO\ CH_2CH_2CO_2C_2H_5 \xrightarrow{CH_3Mg\ I}$$

Levulinic acid

Ethyl Levulinate

Isocaprolactone

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[1] Thesis, C. K. Hewes, 1914, U. of Ill.

The isocaprolactone was then treated as described in the original process to prepare the dimethylcyanocarboxethylcyclopentanone.

In the present work it was decided to use the ethyl ester of γ-chloro-isocaproic acid instead of the γ-bromo ester which was used in the original synthesis. An attempt was made to prepare this by decomposing the addition compound formed by the levulinic ester and methyl magnesium iodide, by means of dry hydrochloric acid gas. A tarry mass was obtained which did not yield any γ-chloroester on distillation. The γ-chloroester was prepared in a manner exactly analogous to that used in the preparation of the γ-bromoester. The advantage in using the chloroester is that it can be distilled under diminished pressure, while the bromoester cannot be distilled without decomposition. For this reason a purer product would be expected from the γ-chloroester. In the first condensation of the γ-chloroester and cyanacetic ester carried out, the yield of the ketone was about ten per cent of the weight of the chloroester used. In the other trials a gummy residue was obtained in the condensation and the yield of ketone was only about one per cent of the weight of the chloroester used.

Noyes and Hewes[1] began a study of the derivatives of dimethylcyanocarboxethylcyclopentanone by attempting to prepare the oxime. They refluxed an alcoholic solution of the ketone with the calculated amount of hydroxylamine hydrochloride and just enough sodium hydroxide to remove the hydrochloric acid. They obtained a white crystalline substance which melted partly at 104° and partly

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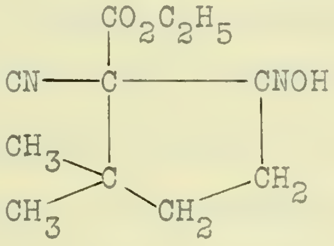
[1] Thesis of C. K. Hewes, U. of Ill. 1914, page 21.

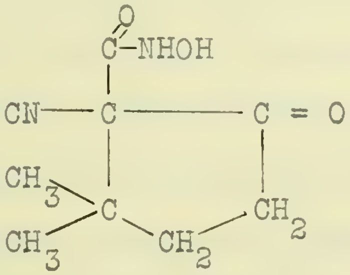
at 118°. One analysis for nitrogen seemed to show that this compound was a mixture of the "syn" and "anti" oximes of dimethylcyanocarboxethylcyclopentanone.

On hydrolysis of this compound with sodium hydroxide a product was obtained which melted at 127°-129°. A calcium salt was prepared and analysed but this did not correspond to the composition calculated for the calcium salt of dimethyl-dicarboxylic-cyclopentanone oxime.

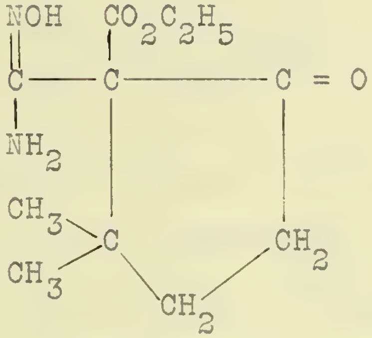
The hydroxylamine might react with either the carbonyl groups, the nitrile group, or the carboxethyl group in the dimethy-cyano-carboxethyl-cyclopentanone. The reaction of the hydroxylamine with the carbonyl group would yield the oxime with the formula:



The reaction of the hydroxylamine with an ester group yields a hydroxamic acid. This type of reaction is not very common and would not be expected in this particular case. If this reaction occurred the compound formed would have the formula:



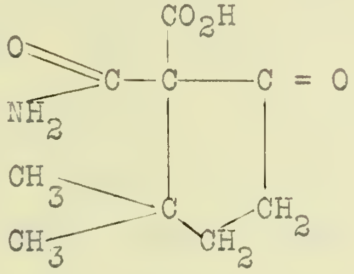
The reaction of hydroxylamine with a nitrile group yielding an amide oxime is quite common in both the aliphatic and aromatic series. The amide oxime group is easily saponified even by boiling with water for some time, giving an amide and regenerating the hydroxylamine. The amide oxime derivative of dimethyl-cyano-carboxethyl-cyclopentanone would have the formula:



In attempting to repeat the preparation of the oxime in the manner described the same type of product was obtained. It melted partly at 104° and completely at 118°. An attempt was made to separate this product into two compounds with definite melting points. On account of the small amount of material available no results in this direction were obtained. However, on recrystalling from water several times a product was obtained which melted almost entirely between 104° and 110°. The product was analysed for carbon, hydrogen, and nitrogen. The analyses for nitrogen were not altogether satisfactory but taken with those for carbon and hydrogen seem to show that the compound obtained by the action of the hydroxylamine hydrochloride on dimethyl-cyano-carboxethyl-cyclopentanone is not the oxime but is the amide oxime. The range in melting point and the low values obtained in the nitrogen determina-

tions were probably due to some unchanged ketone which had not been separated from the amide oxime.

The amide oxime on hydrolysis with sodium hydroxide would yield the compound:



whose calcium salt would have almost the same composition as that which Mr. Hewes obtained by the hydrolysis of the so-called oxime. This compound would probably not be very stable, but would break down farther to yield the same type of products obtained by the hydrolysis of the original ketone.

III. Experimental

Preparation of the Ethyl Ester of Levulinic Acid.[1]

200 grams of levulinic acid were dissolved in 600 grams of absolute alcohol and 14 grams of dry hydrochloric acid gas were passed into the solution. The solution was then refluxed on the water bath for five to six hours, the alcohol was rapidly distilled off, and the ester distilled under diminished pressure. The portion boiling at 98°-104° under 17-20mm. pressure or at 110°-115° under 25-30mm. pressure was collected. Yield 227 grams or 90% of the theory.

Attempt to Prepare the Ethyl Ester of γ-Chloro-isocaproic Acid Directly from Levulinic Ester.[2]

30 grams of methyl iodide were mixed with an equal volume of anhydrous ether and the solution slowly dropped thru a condenser into a flask containing 4.86 grams of freshly polished and dried magnesium ribbon. The flask was warmed slightly to put the last traces of magnesium in solution.

The methyl-magnesium-iodide solution prepared in this manner was slowly siphoned into a flask containing 28.8 grams of levulinic ester and 25cc. of anhydrous ether. The reaction was quite vigorous and an efficient condenser was needed. The addition product formed was insoluble in the ether and separated as a gummy mass. The mass was allowed to stand over night, then 10cc. of absolute alcohol were added and dry hydrochloric acid gas passed

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1. Fischer and Spier. - Ber. d. Chem. Ges. (1895) 28, 3252.
2. Thesis C. K. Hewes. U. of Ill. 1914.

into the mixture until it was saturated. It was then allowed to stand for 24 hours. The mass was treated with ice water and the aqueous solution extracted with ether. The ether extract was dried with anhydrous Na_2SO_4 and the ether distilled off. A black gummy residue weighing 20 grams remained in the flask. When an attempt was made to distill this product it decomposed even under a pressure of 3mm. No pure γ-chloroester was obtained.

Preparation of Isocaprolactone[1]

A solution of methyl-magnesium-iodide was prepared by dropping 227 grams of methyl iodide dissolved in an equal volume of anhydrous ether, thru an upright condenser into a flask containing 38.3 grams of freshly polished and dried magnesium ribbon, covered with 300cc. of anhydrous ether. A crystal of iodine was added to start the reaction which then proceeded rapidly.

The methyl-magnesium-iodide solution prepared in this manner was cooled and then slowly siphoned thru an upright condenser into a flask containing 227 grams of levulinic ester and 500cc. of anhydrous ether. The reaction was vigorous. The addition product separated as a gummy mass. After all the methyl-magnesium iodide was added the solution was refluxed until the reaction appeared to be complete. This required about two hours. The solution was cooled and treated with 100cc. of 1-1 H_2SO_4 solution and crushed ice. The aqueous solution was extracted several times with ether, the ether extract shaken three times with 5% H_2SO_4, and dried with anhydrous Na_2SO_4. The ether was distilled off and the residue fractionally distilled. 60 grams

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[1] Thesis of C. K. Hewes. U. of Ill.1914.

of isocaprolactone boiling at 205°-210° under atmospheric pressure were obtained. This is about 33% of the theory.

Preparation of the Ethyl Ester of γ-Chloroisocaproic Acid.[1]

60 grams of isocaprolactone were dissolved in 180cc. of absolute alcohol and the flask containing the solution was placed in an ice bath. Dry hydrochloric acid gas was passed into the solution until it was saturated. About 100 grams were necessary. The solution was allowed to stand for 12-15 hours and then poured on crushed ice. The aqueous solution was extracted several times with low boiling ligroin, the extract washed with sodium chloride solution and dried with anhydrous Na_2SO_4. The ligroin was distilled off under diminished pressure and the γ-chloroester was distilled under a pressure of 12mm. Yield 34 grams of γ-chloroester boiling at 85°-91° under a pressure of 12mm., or 36.3% of the theory.

Preparation of 3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone.[2]

5.54 grams of sodium were dissolved in 75cc. of absolute alcohol and the solution was cooled. Then a mixture of 25.3 grams of ethyl cyanacetic ester and 43 grams of γ-chloroester was added and the whole solution was refluxed until neutral to litmus. The reaction was completed in about two hours. The solution was cooled and poured into water slightly acidified with sulphuric acid. The aqueous solution was extracted several times with ether and the extract washed several times with concentrated salt (NaCl) solution.

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[1] Noyes, J. Am. Chem. Soc. (1901) 23, 394.

[2] Noyes, Am. Chem. J. (1889) 22, 260.

The extract was dried with anhydrous Na_2SO_4 and the ether distilled off. The by-products of the reaction were distilled off under a pressure of 15-20mm. A reddish brown residue remained in the flask. This residue was recrystalled from alcohol and a white crystalline substance melting at 148.3° was obtained. Yield 3 grams or about 10% of the weight of the γ-chloroester used. The ketone gives no red color with $FeCl_3$ solution.

Preparation of the Amide Oxime derivate of 3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone.[1]

2.09 grams of the ketone and 0.695 grams of hydroxylamine hydrochloride were dissolved in absolute alcohol and 1.34cc. of sodium hydroxide solution (3cc.= 1 gr. NaOH) were added. The solution was refluxed for eight hours on the water bath. The NaCl was filtered off from the hot solution. The alcoholic solution was allowed to cool and no unchanged ketone separated, showing that practically all the ketone was used up in the reaction. The alcohol was allowed to evaporate spontaneously and large cubical crystals separated. These crystals were washed with cold water and dried. Yield 1.4 grams of a substance melting partly at 104° and partly at 118°-119°.

An attempt was made to separate these two fractions by means of fractional crystallization. Trials were made using carbon tetrachloride, benzene, ether, and dilute alcohol but no distinct separation was obtained. Considerable material was used up in these experiments.

An analysis for nitrogen was made on the material that

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[1] Thesis, C. K. Hewes. U. of Ill. 1914.

remained after the attempts at separation. 0.1322 grams of the substance gave 12.9cc. of nitrogen gas measured over 40% KOH at 28° and 738mm. pressure.

Calculated for $C_{11}H_{18}O_4N_2$ N = 11.56%

Found N = 10.50%.

A second preparation was made in the same manner as the preceding but a more definite product was obtained. This preparation melted at 112°-115°. 0.1004 grams of this substance gave 10.6cc. of nitrogen gas measured over 40% KOH at 27° and 727.3mm. (corrected for the vapor pressure of the KOH).

Calculated for $C_{11}H_{18}O_4N_2$ N = 11.56%

Found N = 11.50%.

In the preceding work the assumption was made that the product obtained would be the oxime. The low nitrogen values pointed to the fact that the amide oxime was really formed. A third preparation was made and a complete analysis for carbon, hydrogen, and nitrogen was made. The material was made in the same manner as before except it was crystallized from hot water. The substance melted from 104° to 118° but most of the material melted about 110°. An alcoholic solution of the substance gave a deep red color with $FeCl_3$ solution.

0.1508 grams of material gave 0.3024 grams of carbon dioxide and 0.1062 grams of water.

0.1028 grams of material gave 9.7cc. of nitrogen gas measured over 40% KOH at 17° and 745mm. pressure.

			C	H	N
Calculated for	original ketone	$C_{11}H_{15}O_3N$	63.12%	7.22%	6.69%
"	" Oxime	$C_{11}H_{16}O_3N_2$	58.89%	7.19%	12.49%
"	" Hydroxamic acid	$C_9H_{12}O_3N_2$	55.10%	6.12%	14.28%
"	" Amide Oxime	$C_{11}H_{18}O_4N_2$	54.51%	7.49%	11.56%
Found			54.69%	7.88%	10.90%

The results of these analyses show that undoubtedly the hydroxylamine hydrochloride reacts with the nitrile group of the 3,3 dimethyl-2-cyano-2-carboxethyl-cyclopentanone to form the amide oxime derivative.